REMARKS

Claims 59-64 are pending in the subject application. By this amendment applicant has added new claim 65. Support for new claim 65 may be found in the specification at, inter alia, page 8, lines 1-4. Applicant maintains that these amendments raise no issue of new matter. Accordingly, claims 59-65 will be pending upon entry of this Amendment.

Rejection Under 35 U.S.C. § 103(a)

On page 2 of the April 11, 2005 Office Action, the Examiner rejected claims 59-64 under 35 U.S.C. §103(a) as allegedly being unpatentable over Metcalf et al. (Metcalf). The Examiner alleged that Metcalf teaches a method of using oxandrolone for nitrogen retention wherein the daily amounts of oxandrolone are from 5 mg, 10 mg, 20 mg, and up to 150 mg and that oxandrolone was taken as single dose daily. The Examiner also alleged that Metcalf teaches that the optimal dosage is about 25 mg or 30 mg a day.

Applicant's Reply

In response to the Examiner's rejection, applicant respectfully traverses on the ground that a prima facie case of obviousness has not been established.

Briefly, the pending claims are drawn to pharmaceutical compositions comprising oxandrolone wherein the oxandrolone is present in the composition in specific amounts and ranges of amounts. Claim 63 and new dependent claim 65 require the composition to be in solid form.

Metcalf reports on the effects of oxandrolone administration on nitrogen retention in human subjects.

Under MPEP §2143, to establish a *prima facie* case of obviousness,

the Examiner must demonstrate three things with respect to each claim. First, the cited reference must teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to modify the teachings of the cited reference at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

1. Metcalf does not teach or suggest every element of the claim

Metcalf does not disclose administration of a pharmaceutical composition comprising the amounts of oxandrolone as recited in the pending claims. Further, as noted by the Examiner, Metcalf does not disclose whether the oxandrolone comprises a pharmaceutical carrier. Most importantly, Metcalf does not discuss whether the oxandrolone was in solid form, or whether each patient received the respective dose of oxandrolone as a single pharmaceutical composition or as multiple compositions of, e.g. 2.5 mg.

On page 66, Metcalf states that "We are grateful for the support of these studies from G.D. Searle and Company…." As noted on page 1 and 15 in reference 23 of the attached Information Disclosure Statement, the Physician's Product Brochure No. 43 for ANAVAR® Brand of Oxandrolone indicates that the oxandrolone available in 1964 from G.D. Searle and Company was available in tablets containing 2.5 mg of oxandrolone.

Because Metcalf only discloses the total dosage of oxandrolone administered to each patient, the actual pharmaceutical composition Metcalf used is unspecified. However, based on the reference to G.D. Searle and Company, Metcalf likely administered to the patients multiple dosages of the 2.5 mg tablets available from G.D. Searle and Company.

Accordingly, Metcalf does not teach or suggest every element of the claimed invention.

2. One of ordinary skill would not have been motivated to modify the teachings of Metcalf at the time of the invention.

MPEP § 2143.01 provides: "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art."

Metcalf unambiguously teaches that the "optimum" dosage of oxandrolone is 25 to 30 mg/day (page 63 of Metcalf). Applicant, on the other hand, claims a pharmaceutical composition having a dosage ranging from 7.5 mg, specific ranges of 7.5 mg to 20 mg, and specific dosages of 10 mg (claim 61) and 20 mg (claim 62), none of which are suggested by Metcalf.

Indeed, Metcalf teaches away from the claimed pharmaceutical compositions by its express teaching that a dosage of 25 mg to 30 mg (daily) is an optimum dosage.

MPEP § 2143.01 further provides that, "[I]f a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification" In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

On page 60, Metcalf discloses that patients receiving dosages of oxandrolone lower than 25-30 mg/day exhibited variable responses. Thus, preparing pharmaceutical compositions having the lower dosages of oxandrolone recited in the pending claims would be

unsatisfactory for Metcalf's stated purpose of nitrogen retention.

Accordingly, one of ordinary skill would not have been motivated to prepare the claimed compositions from the teachings of Metcalf.

3. There would have not been a reasonable expectation that the claimed invention would succeed.

Metcalf, at most, motivated preparation of a pharmaceutical composition containing 25 to 30 mg of oxandrolone as the active ingredient. There is no rationale in Metcalf to prepare pharmaceutical compositions having the claimed dosages of oxandrolone. Without the benefit of hindsight and the applicant's disclosure, the preparation of pharmaceutical compositions having lower dosages would have been illogical based on Metcalf.

Finally, if Metcalf could motivate applicant's claimed invention there would not be such a long period of time between Metcalf (published in 1965) and the effective filing of the subject application (filed in 1992). No reference has been cited by the Examiner that teaches or even suggests a pharmaceutical composition containing 7.5 mg of oxandrolone as the active ingredient, or for that matter any pharmaceutical composition containing more than 2.5 mg of oxandrolone.

Accordingly, no *prima facie* case of obviousness has been made. As discussed, Metcalf does not teach or suggest every element of the claim, neither does any other reference of record. Accordingly, the obviousness rejection should be withdrawn.

Conclusion

For each of the above reasons, independently discussed above, applicant respectfully submits that all pending claims of the subject application are patentable over Metcalf.

FOURTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. § 1.56 applicant directs the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit A**) and attached hereto as **Exhibits 1-61.**

Applicant is filing this Fourth Supplemental Information Disclosure Statement to supplement the Information Disclosure Statement filed on January 18, 2002, the Supplemental Information Disclosure Statement filed on October 9, 2003, the Supplemental Information Disclosure Statement filed on March 5, 2004, and the Third Supplemental Information Disclosure Statement filed on May 14, 2004. Applicant files this Fourth Supplemental Information Disclosure Statement under C.F.R. §1.97(c)(2), before the mailing of a final office action on the merits accompanied by the fee of ONE HUNDRED EIGHTY DOLLARS ($180.00) set forth in 37 C.F.R. §1.17(p). Accordingly, applicant requests that this Fourth Supplement Information Disclosure Statement be considered.

1. U.S. Patent No. 3,128,283 issued April 7, 1964, Pappo (**Exhibit 1**);

2. U.S. Patent No. 5,461,030, issued October 24, 1995, Lindenbaum (**Exhibit 2**);

3. U.S. Patent No. 5,532,230, issued July 2, 1996, Daynes et al. (**Exhibit 3**);

4. U.S. Patent No. 5,922,701, issued July 13, 1999, Araneo (**Exhibit 4**);

5. U.S. Patent No. 6,828,313, issued December 7, 2004, Fishbein, (**Exhibit 5**);

6. Protest Under 37 C.F.R. §1.291(a) filed on October 18, 1999 with the United States Patent and Trademark Office in connection with U.S. Serial No. 08/244,988, pp. 1-7, including a cover sheet, a Form PTO-1449, and Exhibits A-E, (**Exhibit 6**);

7. March 2, 2000 Decision on Protest Under 37 C.F.R. §1.291(a) in connection with U.S. Serial No. 08/244,988, pp. 1-2, including a cover sheet, a Form PTO-892, Information on Submitting an INDA (2 pages), and a copy of 21 C.F.R. 312 (39 Pages), (**Exhibit 7**);

8. May 14, 1999 letter from the Department of Health and Human Services, Center For Drug Evaluation and Research, Rockville, Maryland, providing a "Copy of All Disclosable Approval Information For the Product Oxandrin, Manufactured by Biotechnology General," 30 pages (**Exhibit 8**).

9. Albanese, A.A., Lorenze, E.J., and Orto, L.A., (May 15, 1962) Nutritional and Metabolic Effects of Some Newer Steroids, Oxandrolone and Triamcinolone, New York State J. Med. 62:1607-1613, (**Exhibit 9**);

10. Albanese et al., (1970), "Steroid and Dietary Effects On Blood Lipids In Elderly Persons," *Nutrition Reports International*, Vol. 1, No. 4, pp. 231-242 (**Exhibit 10**);

11. Bailey, R.O., Turok, D.I., Jaufmann and Singh, J.K. (1987). Myositis and acquired immunodeficiency syndrome. Hum. Path. 18:749-751, (**Exhibit 11**);

12. Berger, J.R., (1991). Personal communication between Dr. Berger and Dr. Dudley of Gynex (letter dated July 6, 1991), (**Exhibit 12**);

13. Berkowitz, D., Clinical Investigator's Report, April 25,1962, (**Exhibit 13**);

14. Bessen, L.J., Greene, J.B., Louie, E., Seitzman, P., and Weinberg, H. (1988). Severe polymyositis-like syndrome associated with zidovudine therapy in AIDS and ARC. N. Eng. J. Med. 318:708, (**Exhibit 14**);

15. Blizzard, R.M., Hindmarsh, P.C. and Stanhope, R. (1991). Oxandrolone therapy: 25 years experience. Growth, Genet. Hor. 7:1-7, (**Exhibit 15**);

16. Chelbowski, R.T., Grosvenor, M.B., Bernhard, N.H., Morales, L.S. and Bulcavage, L.M. (1989). Nutritional status, gastrointestinal dysfunction and survival in patients with AIDS. Am. J. Gastroent. 84:1288-1293, (**Exhibit 16**);

17. Chernoff, D. (1990). Myositis in HIV-infected patients. In the AIDS Knowledge Base, Cohen, P.T., Sande, M.A. and Volberding, P.A. (eds.). Waltham, The Medical Publishing Group, pp. 5.14. 1-2, (**Exhibit 17**);

18. Dalakas, M.C., Pezeshkpour, G.H., Gravell, M. and Sever, J.L. (1986). Polymyositis associated with AIDS retrovirus. J. Amer. Med. Assoc. 256:2381-2383, (**Exhibit 18**);

19. Demling et al., (1996), "Use of Anticatabolic Agents For Burns," *Current Opinion in Critical Care*, Vol. 2, pp. 482-491 (**Exhibit 19**);

20. Demling, (1999), "Comparison of the Anabolic Effects and Complications of Human Growth Hormone and the Testosterone Analog, Oxandrolone, After Severe Burn Injury," *Burns*, Vol. 25, pp. 215-221 (**Exhibit 20**);

21. Demling and DeSanti, (2001), "The Rate of Restoration of Body Weight After Burn Injury, Using the Anabolic Agent Oxandrolone, is not Age Dependent," *Burns*, Vol. 17, pp. 46-51 (**Exhibit 21**);

22. Draft of G.D. Searle & Co., (1962), Physicians' Product Brochure No. 43, "*ANAVAR® Brand of Oxandrolone, For Protein Tissue Building and Anabolism,*" 16 pages with a 5 page insert (**Exhibit 22**);

23. FDA approved Physician's Product Brochure No. 43 for ANAVAR® Brand of Oxandrolone, including Package Insert, G.D. Searle (1964), (**Exhibit 23**);

24. Fox et al., (1962), "Oxandrolone: A Potent Anabolic Steroid of Novel Chemical Configuration," *J. Clin. Endocrinol. Metab.*, Vol. 22, pp. 921-924 (**Exhibit 24**);

25. Garlick et al., (October 1988), "Regulation of Muscle Protein Turnover: Possible Implications For Modifying the Responses to Trauma and Nutrient Intake," in *Bailliere's Clinical Gastroenterology*, Bailliere Tindall, London/Philadelphia/ Sydney/Tokyo/Toronto, Burns ed., Vol. 2, No. 4, pp. 915-940 (**Exhibit 25**);

26. Gold, E.M., Clinical Investigator's Report, May 31, 1962,(**Exhibit 26**);

27. Gonzales, M.F., Olney, R.K., So, Y.T., Greco, C.M., et al. (1988). Subacute structural myopathy associated with human immunodeficiency virus infection. Arch. Neurol. 45:585-587, (**Exhibit 27**);

28. Gorard, D.A., Henry, K., and Guiloff, R.J. (1988). Necrotizing myopathy and zidovudine. Lancet. 1:1050-1051, (**Exhibit 28**);

29. Haupt et al., (1984), "Anabolic Steroids: A Review of the Literature," *The American Journal of Sports Medicine*, Vol. 12, No. 6, pp. 469-484 (**Exhibit 29**);

30. Heller, C.G., Clinical Investigator's Report, June 20, 1962, (**Exhibit 30**);

31. Hellerstein, M.K., J. Mudie, H. and Viteri, F. (1990). Current Approach to the treatment of human immunodeficiency virus-associated weight loss: pathophysiologic considerations and emerging management strategies. Sem. Oncol. 17:17-33, (**Exhibit 31**);

32. Hernon et al., (June 1987), "Treatment of Burns," in *Current Problems in Surgery*, Year Book Medical Publishers, Inc., Chicago, Ravitch et al., eds., Vol. 24, No. 6, pp. 347-397 (**Exhibit 32**);

33. Hughes, B.J. and Kreig, M. (1988). Steroid receptors and the muscular system. In, Steroid Receptors and Disease, Sheridan, P.J. Blum, K. and Trachtenberg, M.C. (eds). Marcel Dekker, Inc., New York, pp. 415-433, (**Exhibit 33**);

34. Jones, R.W.A., El Bishti, M.M., Bloom, S.R., Burke, J., Carter, J.E., et al (1980). The effects of anabolic steroids on growth, body composition, and metabolism in boys with chronic renal failure on regular hemodialysis. J. Pediat. 97:559-566, (**Exhibit 34**);

35. Karim et al., (1973), "Oxandrolone Disposition and Metabolism In Man," *Clin. Pharmacol. Ther.* Vol. 14, No. 5, pp. 862-869 (**Exhibit 35**);

36. Kasler, M.H., Clinical Investigator's Report, March 16, 1962,

(**Exhibit 36**);

37. Kotler, D.P., Wang, J. and Pierson, R.N. (1985). Body composition studies in patients with acquired immunodeficiency syndrome. Am. J. Clin. Nutr. 42:1255-1265, (**Exhibit 37**);

38. Kotler, D.P., Tierney, A.R., Wang, J., and Pierson, R.N. (1989). Magnitude of body-cell-mass depletion and the timing of death wasting in AIDS. Am. J. Clin. Nutr. 50:444-447, (**Exhibit 38**);

39. Kowalewski and Heron, (1970), "Effect of Thermal Injury on Excretion of Hydroxyproline In Rats, Treated Or Not With An Anabolic Androgen," *Acta Endocrinologica*, Vol. 64, pp. 541-547, (**Exhibit 39**);

40. Leevy, C.M., Clinical Investigator's Report, August 24, 1961, (**Exhibit 40**);

41. Marmo et al., (February 1974), "Experimental Analysis of Some Pharmacodynamic Effects Nor-19-Androstenolone Undecylate," *Gazzetta Medica Italiana*, (in Italian with English Translation), Vol. 133, No. 2, pp. 47-56 (**Exhibit 41**);

42. Masse, R.B.H., Ayotte, C. and Dugal, R. (1989). Studies on anabolic steroids II - Gas chromatographic/mass spectrometric characterization of oxandrolone urinary metabolites in man. Biomed. Environ. Mass Spectrom. (England) 18:429-438, (**Exhibit 42**);

43. Mendenhall, C.L., Anderson, S., Garcia-Pont, P., Goldberg, S., et al. (1984). Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prenisolone. N. Eng. J. Med. 311:1464-1470, (**Exhibit 43**);

44. Mendenhall, C.L., Grossman, C.J., Roselle, G.A., et al. (1990). Anabolic steroids effects on immune function: differences between analogues. J. Steroid Biochem. Molec. Biol. 37:71-76, (**Exhibit 44**);

45. Mensch, M., Clinical Investigator's Report, August 23, 1962, (**Exhibit 45**);

46. Metcalf, W., Clinical Investigator's Report, July 14, 1961, (**Exhibit 46**);

47. Meyers, F.H., Jawetz, E. and Goldfien, A. (1980). Review of Medical Pharmacology. California: Lange Medical Publications, p. 415, (**Exhibit 47**);

48. O'Shea et al., (December 1970), "Biochemical and Physical Effects of An Anabolic Steroid In Competitive Swimmers and Weightlifters," *Nutrition Report International,* Vol. 2, No. 6, pp. 351-361 (**Exhibit 48**);

49. Pan, C.S., Inadomi, D.W., Laidlaw, S.A., Jones, M.R., and Kopple, J.D. (1984). Oxandrolone enhances muscle protein synthesis in acutely uremic rats. Kidney Intl. 25:236, (**Exhibit 49**);

50. Paulsen, C.A., Clinical Investigator's Report, March 9,1962, (**Exhibit 50**);

51. Physicians' Desk Reference, (1984), 38th Edition, Huff et al. eds., pp. 1840-1841 (**Exhibit 51**);

52. Roubenoff and Kehayias, (June 1991), "The Meaning and Measurement of Lean Body Mass," *Nutrition Reviews,* Vol. 49, No. 6, pp. 163-175 (**Exhibit 52**);

53. Ruffin, J.M., Clinical Investigator's Report, March 20, 1962, (**Exhibit 53**);

54. Selye, (1970), "Prevention of Indomethacin-Induced Intestinal Ulcers by Various Catatoxic Steroids," *Exp. Med. Surg.*, Vol. 28, pp. 169-78 (**Exhibit 54**);

55. Simpson, D.M. and Bender, A.N. (1988). Human immunodeficiency virus-associated myopathy: analysis of 11 patients. Ann. Neurol. 24:79-84, (**Exhibit 55**);

56. Solymoss et al., (1971), "Protection by Spironolactone and Oxandrolone Against Chronic Digitoxin or Indomethacin Intoxication," *Toxicol. Appl. Pharmacol.*, Vol. 18, pp. 586-92 (**Exhibit 56**);

57. Stern, R., and Gold, J. and DiCarlo, E.F. (1987). Myopathy complicating the acquired immune deficiency syndrome. Muscle Nerve. 10:318-322, (**Exhibit 57**);

58. Tchekmedyian, (1993), "Clinical Approaches to Nutritional Support in Cancer," *Current Opinion in Oncology,* Vol. 5, pp. 633-638 (**Exhibit 58**);

59. Wilson, (1990), "Androgens," in *Goodman and Gilman's, The Pharmacological Basis of Therapeutics*, Eighth Edition, Pergamon Press, New York, pp. 1413-1430 (**Exhibit 59**);

60. Wolfe, (1986), "Nutrition and Metabolism in Burns," in, *Critical Care State of the Art*, Society of Critical Care Medicine, Fullerton, California, Chernow B. and Shoemaker W.C. eds., Vol. 7, pp. 19-61 (**Exhibit 60**); and

61. Woolery, J.W., Clinical Investigator's Report, April 27,1962, (**Exhibit 61**).

Reference items 20-21 (**Exhibits 20-21**) are copies of documents which were disclosed in applicant's May 14, 2004 Third Supplemental Information Disclosure Statement. In the initialed Form PTO-1449 attached to the June 17, 2004 Office Action, Examiner Travers indicated that Exhibits 20 and 21 above were not received with the Third Supplemental Information Disclosure Statement. Therefore, applicant is hereby submitting new copies of Exhibits 20 and 21 for the Examiner's consideration.

In addition, applicant notes that the form PTO-1449s filed on January 18, 2002 and October 9, 2003, in the subject application have not been returned to applicant with the Examiner's initials indicating consideration of the references cited therein. Copies of these forms filed on January 18, 2002 and October 9, 2003 are attached hereto as **Exhibit B** and **Exhibit C** respectively. Applicant respectfully requests that the Examiner consider the references, and then initial the citations of the references listed on the forms PTO-1449 filed on January 18, 2002 and October 9, 2003 and return copies of the initialed forms for applicant's files.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed fee of $1020.00 for a three-month extension of time and $180.00 for filing the Fourth Supplemental Information Disclosure Statement before the mailing of the final office action both of which are enclosed in a check for $1200.00, is deemed necessary in connection with the filing of this Amendment and Fourth Supplemental Information Disclosure Statement. If any such fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Gary J. Gershik 10/11/05

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